JUN 19 2000

NDA 11-808/ SLR-175
NDA 17-923 / SLR-048

Novartis
Attention: James Rawis, Pharm.D.
Assistant Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936

Dear Dr. Rawls:

Please refer to your supplemental new drug applications of April 5, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mellaril (thioridazine HCL) Tablets, Oral Suspension, and Oral Solution.

We acknowledge receipt of your submissions of April 19, 2000, May 15, 2000, and May 19, 2000.

These supplemental new drug applications provide for labeling changes necessary to adequately warn prescribers of dose-related prolongation of the QTc interval associated with thioridazine and the potential for serious cardiac arrhythmias.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert)...

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 11-808/SLR-175, 17-923/SLR-048." Approval of these submissions by FDA is not required before the labeling is used.

Please also submit a final copy, identical to the agreed upon enclosed draft, of the "Dear Health Care Practitioner Letter" when it is issued to physicians and others responsible for patient care. You should submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2

FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Steven D. Hardeman, R.Ph., Regulatory Project Manager, at (301) *594-5525.*

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures (2)

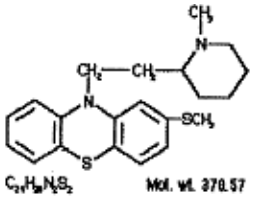
NOVARTIS

T2000-34
89001902

Mellaril®
(thioridazine HCl) Tablets, USP
(thiondazine HCl) Oral Solution, USP
Mellaril-S®
(thioridazine) Oral Suspension, USP
For Oral Administration
Rx only

WARNING
MELLARIL (THIORIDAZINE HCl) HAS BEEN SHOWN TO PROLONG THE QTc INTERVAL IN A DOSE RELATED MANNER, AND DRUGS WITH THIS POTENTIAL, INCLUDING MELLARIL, HAVE BEEN ASSOCIATED WITH TORSADE DE POINTES-TYPE ARRHYTHMIAS AND SUDDEN DEATH. DUE TO ITS POTENTIAL FOR SIGNIFICANT, POSSIBLY LIFE-THREATENING, PROARRHYTHMIC EFFECTS, MELLARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF TREATMENT WITH OTHER ANTIPSYCHOTIC DRUGS, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. (SEE WARNINGS, CONTRAINDICATIONS, AND INDICATIONS).

DESCRIPTION
Mellaril (thioridazine HCl) is 2-methylmercapto-10-[2-(N-methyl-2-piperidyl) ethyl] phenothiazine.



10mg, 15mg, 25mg, 50mg, 100mg, 150mg, and 200mg Tablets
Active Ingredient: thioridazine HCl, USP
10mg Tablets
Inactive Ingredients: acacia, calcium sulfate dihydrate, camauba wax, D&C Yellow #10, FD&C Blue #1, FD&C Yellow #6, gelatin, lactose, methylparaben, povidone, propylparaben, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.
15mg Tablets
Inactive Ingredients: acacia, calcium sulfate dihydrate, camauba wax, D&C Red #7, gelatin, lactose, methylparaben, povidone, propylparaben, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.
25mg Tablets

Inactive Ingredients: acacia, calcium sulfate dihydrate, camauba wax, gelatin, lactose, methylparaben, povidone, propylparaben, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, synthetic iron oxide, talc, titanium dioxide, and other ingredients.

50 mg Tablets

Inactive Ingredients: acacia, calcium sulfate dihydrate, carnauba wax, gelatin, lactose, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

100 mg Tablets

Inactive Ingredients: acacia, calcium sulfate dihydrate, carnauba wax, D&C Yellow #10, FD&C Blue #1, FD&C Blue #2, FD&C Yellow #6, lactose, methylparaben, povidone, propylparaben, sodium benzoate, sorbitol, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

150 mg Tablets

Inactive Ingredients: acacia, calcium sulfate dihydrate, camauba wax, D&C Yellow #10, FD&C Green #3, FD&C Yellow #6, lactose, methylparaben, povidone, propylparaben, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

200 mg Tablets

Inactive Ingredients: acacia, ammonium calcium alginate, calcium sulfate dihydrate, camauba wax, colloidal silicon dioxide, D&C Red #7, lactose, magnesium stearate, methylparaben, povidone, propylparaben, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide, and other ingredients.

30 mg/ml and 100 mg/ml Oral Solution (Concentrate) Active Ingredient: thioridazine HCI, USP

30 mg/mL Oral Solution (Concentrate)

Inactive Ingredients: alcohol, 3.0%, flavor, methylparaben, propylparaben, purified water, and sorbitol solution. May contain sodium hydroxide or hydrochloric acid to adjust the pH.

100 mg/mL Oral Solution (Concentrate)

Inactive Ingredients: alcohol, 4.2%, flavor, glycerin, methylparaben, propylparaben, purified water, sorbitol solution, and sucrose. May contain sodium hydroxide or hydrochloric acid to adjust pH.

5 mg/mL and 20 mg/mL Oral Suspension

Active Ingredient: each mL contains thioridazine, USP, equivalent to 5 mg and 20 mg thioridazine HCI, USP, respectively.

5mg/mL Oral Suspension

Inactive Ingredients: carbomer 934, flavor, polysorbate 80, purified water, sodium hydroxide, and sucrose.

20mg/mi Oral Suspension

Inactive Ingredients: carbomer 934, D&C Yellow #10, FD&C Yellow #*6,* flavor, polysorbate 80, purified water, sodium hydroxide, and sucrose.

CLINICAL PHARMACOLOGY

The basic pharmacological activity of Mellaril(thioridazine HCI) is similar to that of other phenothiazines, but is associated with minimal extrapyramidal stimulation.

However, thioridazine has been shown to prolong the QTc interval in a dose-dependent fashion. This effect may increase the risk of serious, potentially fatal, ventricular arrhythmias, such as torsade de pointes-type arrhythmias. Due to this risk, Mellaril is indicated only for schizophrenic patients who have not been responsive to or cannot tolerate other antipsychotic agents (see WARNINGS and CONTRAINDICATIONS). However, the prescriber should be aware that Mellaril has not been systematically evaluated in controlled trials in treatment refractory schizophrenic patients and its efficacy in such patients is unknown.

INDICATIONS

Mellaril® (thioridazine HCI) is indicated for the management of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. Due to the risk of significant, potentially life-threatening, proarrhythmic effects with Mellaril treatment, Mellaril should be used only in patients who have failed to respond adequately to treatment with appropriate courses of other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse

effects from those drugs. Consequently, before initiating treatment with Mellaril, it is strongly recommended that a patient be given at least 2 trials, each with a different antipsychotic drug product, at an adequate dose, and for an adequate duration (see WARNINGS and CONTRAINDICATIONS).
However, the prescriber should be aware that Mellaril has not been systematically evaluated in controlled trials in treatment refractory schizophrenic patients and its efficacy in such patients is unknown.

CONTRAINDICATIONS
Mellaril® (thioridazine HCl) use should be avoided in combination with other drugs that are known to prolong the QTc interval and in patients with congenital long QT syndrome or a history of cardiac arrhythmias. Reduced cytochrome P450 2D6 isozyme activity drugs that inhibit this isozyme (e.g., fluoxetine and paroxetine) and certain other drugs (e.g., fluvoxamine, propranolol, and pindolol) appear to appreciably inhibit the metabolism of thioridazine. The resulting elevated levels of thioridazine would be expected to augment the prolongation of the QTc interval associated with Mellaril and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias. Such an increased risk may result also from the additive effect of co-administering Mellaril with other agents that prolong the QTc interval. Therefore, Mellaril is contraindicated with these drugs as well as in patients, comprising about 7% of the normal population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6 (see WARNINGS and PRECAUTIONS).
In common with other phenothiazines, Mellaril is contraindicated in severe central nervous system depression or comatose states from any cause including drug induced central nervous system depression (see WARNINGS). It should also be noted that hypertensive or hypotensive heart disease of extreme degree is a contraindication of phenothiazine administration.

WARNINGS

Potential for Proarrhythmic Effects
DUE TO THE POTENTIAL FOR SIGNIFICANT, POSSIBLY LIFE-THREATENING, PROARRHYTHMIC EFFECTS WITH MELLARIL(THIORIDAZINE HCI) TREATMENT, MELLARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF TREATMENT WITH OTHER ANTIPSYCHOTIC DRUGS, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH MELLARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE, AND FOR AN ADEQUATE DURATION. MELLARIL HAS NOT BEEN SYSTEMATICALLY EVALUATED IN CONTROLLED TRIALS IN THE TREATMENT OF REFRACTORY SCHIZOPHRENIC PATIENTS AND ITS EFFICACY IN SUCH PATIENTS IS UNKNOWN.

A crossover study in nine healthy males comparing single doses of thioridazine 10 mg and 50 mg with placebo demonstrated a dose-related prolongation of the QTc interval. The mean maximum increase in QTc interval following the 50 mg dose was about 23 msec; greater prolongation may be observed in the clinical treatment of unscreened patients.

Prolongation of the QTc interval has been associated with the ability to cause torsade de pointes-type arrhythmias, a potentially fatal polymorphic ventricular tachycardia, and sudden death. There are several published case reports of torsade de pointes and sudden death associated with thioridazine treatment. A causal relationship between these events and Mellaril therapy has not been established but, given the ability of Mellaril to prolong the QTc interval, such a relationship is possible.

Certain circumstances may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including *1)* bradycardia, 2) hypokalemia, 3) concomitant use of other drugs that prolong the QTc interval, 4) presence of congenital prolongation of the QT interval, and 5) for thioridazine in particular, its use in patients with reduced activity of P450 2D6 or its coadministration with drugs that may inhibit P450 2D6 or by some other mechanism interfere with the clearance of thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

It is recommended that patients being considered for Mellaril treatment have a baseline ECG performed and serum potassium levels measured. Serum potassium should be normalized before initiating treatment and patients with a QTc interval greater than 450 msec should not receive Mellaril treatment. It may also be useful to periodically monitor ECG's and serum potassium during Mellaril treatment, especially during a period of dose adjustment. Mellaril should be discontinued in patients who are found to have a QTc interval over 500 msec.

Patients taking Mellaril who experience symptoms that may be associated with the occurrence of torsade de pointes (e.g., dizziness, palpitations, or syncope) may warrant further cardiac evaluation; in particular, Holter monitoring should be considered.

Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are ***not*** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing

a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.
If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on ***Information for Patients*** and ***ADVERSE REACTIONS.)***
It has been suggested in regard to phenothiazines in general, that people who have demonstrated a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to one may be more prone to demonstrate a reaction to others. Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides.
Physicians should carefully consider benefit versus risk when treating less severe disorders. Reproductive studies in animals and clinical experience to date have failed to show a teratogenic effect with Mellaril. However, in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, Mellaril should be given only when the benefits derived from treatment exceed the possible risks to mother and fetus.

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).
The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.
The management of NMS should include, 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.
If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Central Nervous System Depressants
As in the case of other phenothiazines, Mellaril is capable of potentiating central nervous system depressants (e.g., alcohol, anesthetics, barbiturates, narcotics, opiates, other psychoactive drugs, etc.) as well as atropine and phosphorus insecticides. Severe respiratory depression and respiratory arrest have been reported when a patient was given a phenothiazine and a concomitant high dose of a barbiturate.

PRECAUTIONS
Leukopenia and/or agranulocytosis and convulsive seizures have been reported but are infrequent. MellarIl (thioridazine HCI) has been shown to be helpful in the treatment of behavioral disorders in epileptic patients, but anticonvulsant medication should also be maintained. Pigmentary retinopathy, which has been observed primarily in patients taking larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; examination of the fundus discloses deposits of pigment. The possibility of this complication may be reduced by remaining within the recommended limits of dosage.
Where patients are participating in activities requiring complete mental alertness (e.g., driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually. Female patients appear to have a greater tendency to orthostatic hypotension than male patients. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension in view of the fact that phenothiazines may induce a reversed epinephrine effect on occasion. Should a vasoconstrictor be required, the most suitable are levarterenol and phenylephrine.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent ***in vitro,*** a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Drug Interactions:

Reduced cytochrome P450 2D6 isozyme activity, drugs which inhibit this isozyme (e.g., fluoxetine and paroxetine), and certain other drugs (e.g., fluvoxamine, propranolol, and pindolol) appear to appreciably inhibit the metabolism of thioridazine. The resulting elevated levels of thioridazine would be expected to augment the prolongation of the QTc interval associated with Mellaril and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias. Such an increased risk may result also from the additive effect of co-administering Mellaril with other agents that prolong the QTc interval. Therefore, Mellaril is contraindicated with these drugs as well as in patients, comprising about 7% of the normal population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6 (see WARNINGS and CONTRAINDICATIONS).

Drugs that Inhibit Cytochrome P450 2D6

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25 mg oral dose of thioridazine produced a 2.4-fold higher Cmax and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared to rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of cytochrome P450 2D6 isozyme activity. Thus, this study suggests that drugs that inhibit P450 2D6 or the presence of reduced activity levels of this isozyme will produce elevated plasma levels of thioridazine. Therefore, the co-administration of drugs that inhibit P450 2D6 with Mellaril and the use of Mellaril in patients known to have reduced activity of P450 2D6 are contraindicated.

Drugs that Reduce the Clearance of Mellaril through Other Mechanisms

Fluvoxamine: The effect of fluvoxamine (25 mg bid for one week) on thioridazine steady state concentration was evaluated in 10 male in-patients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased three-fold following co-administration of fluvoxamine. Fluvoxamine and Mellaril should not be co-administered.

Propranolol: Concurrent administration of propranolol (100-800mg daily) has been reported to produce increases in plasma levels of thioridazine (approximately 50%-400%) and its metabolites (approximately 80%-300%). Propranolol and Mellaril should not be co-administered.

Pindolol: Concurrent administration of pindolol and thioridazine have resulted in moderate, dose-related increases in the serum levels of thioridazine and two of its metabolites, as well as higher than expected serum pindolol levels. Pindolol and Mellaril should not be co-administered.

Drugs That Prolong the QTc Interval
There are no studies of the co-administration of Mellaril and other drugs that prolong the QTc interval. However, it is expected that such co-administration would produce additive prolongation of the QTc interval and, thus, such use is contraindicated.

Information for Patients: Patients should be informed that Mellaril® (thioridazine HCl) has been associated with potentially fatal heart rhythm disturbances. The risk of such events may be increased when certain drugs are

given together with Mellaril. Therefore, patients should inform the prescriber that they are receiving Mellaril treatment before taking any new medication.

Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Pediatric Use
See *DOSAGE* section *Pediatric Patients.*

ADVERSE REACTIONS
In the recommended dosage ranges with MeIlaril (thioridazine HCI) most side effects are mild and transient.
Central Nervous System: Drowsiness may be encountered on occasion, especially where large doses are given early in treatment. Generally, this effect tends to subside with continued therapy or a reduction in dosage. Pseudoparkinsonism and other extrapyramidal symptoms may occur but are infrequent. Nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache have been reported but are extremely rare.
Autonomic Nervous System: Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor have been seen.
Endocrine System: Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema have been described.
Skin: Dermatitis and skin eruptions of the urticarial type have been observed infrequently. Photosensitivity is extremely rare.
Cardiovascular System: MeIlaril (thioridazine HCI) produces a dose related prolongation of the QTc interval, which is associated with the ability to cause torsade de pointes-type arrhythmias, a potentially fatal polymorphic ventricular tachycardia, and sudden death (see WARNINGS). Both torsade de pointes-type arrhythmias and sudden death have been reported in association with Mellaril. A causal relationship between these events and Mellaril therapy has not been established but, given the ability of Mellaril to prolong the QTc interval, such a relationship is possible. Other ECG changes have been reported ***(See Phenothiazine Derivatives: Cardiovascular Effects).***
Other: Rare cases described as parotid swelling have been reported following administration of Mellaril.
Post Introduction Reports
These are voluntary reports of adverse events temporally associated with MeIlaril (thioridazine HCI) that were received since marketing, and there may be no causal relationship between Mellaril use and these events: priapism.
Phenothiazine Derivatives
It should be noted that efficacy, indications, and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines. The most common neurological side effects in these patients are parkinsonism and akathisia. There appears to be an increased risk of agranulocytosis and leukopenia in the geriatric population. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:
Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.
Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis.
Blood Dyscrasias: Agranulocytosis, leukopenia, easinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.
Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.
Hepatotoxicity: Jaundice, biliary stasis.
Cardiovascular Effects:

Changes in the terminal portion of the electrocardiogram to include prolongation of the QT interval, depression and inversion of the T wave, and the appearance of a wave tentatively identified as a bifid T wave or a U wave have been observed in patients receiving phenothiazines, including Mellaril . To date, these appear to be due to altered repolarization, not related to myocardial damage, and reversible. Nonetheless, significant prolongation of the QT interval has been associated with serious ventricular arrhythmias and sudden death (see WARNINGS). Hypotension, rarely resulting in cardiac arrest, has been reported.

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the ***WARNINGS*** section and subsequently. The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g., protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk, and extremities. The severity of the syndrome and the degree of impairment produced vary widely.
The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long-term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for neuroleptic drugs may mask the signs of the syndrome.
Neuroleptic Malignant Syndrome (NMS): Chronic use of neuroleptics may be associated with the development of Neuroleptic Malignant Syndrome. The salient features of this syndrome are described in the ***WARNINGS*** section and subsequently. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).
Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.
Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states. More recently, a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosuslike syndrome.

OVERDOSAGE
Many of the symptoms observed are extensions of the side effects described under ***ADVERSE REACTIONS.***
Mellaril (thioridazine HCl) can be toxic in overdose, with cardiac toxicity being of particular concern.
Frequent ECG and vital sign monitoring of overdosed patients is recommended. Observation for several days may be required because of the risk of delayed effects.

Signs and Symptoms
Effects and clinical complications of acute overdose involving phenothiazines may include:

Cardiovascular: Cardiac arrhythmias, hypotension, shock, ECG changes, increased QT and PR intervals, non-specific ST and T wave changes, bradycardia, sinus tachycardia, atrrioventricular block, ventricular tachycardia, ventricular fibrillation, Torsade de pointes, myocardial depression.

Central Nervous System: Sedation, extrapyramidal effects, confusion, agitation, hypothermia, hyperthermia, restlessness, seizures, arefiexia, coma.

Autonomic Nervous System: Mydriasis, miosis, dry skin, dry mouth, nasal congestion, urinary retention, blurred vision.
Respiratory: Respiratory depression, apnea, pulmonary edema.
Gastrointestinal: Hypomotility, constipation, ileus.
Renal: Oliguria, uremia.
Toxic dose and blood concentration ranges for the phenothiazines have not been firmly established. It has been suggested that the toxic blood concentration range for thioridazine begins at 1.0 mg/dL, and 2-8 mg/dL is the lethal concentration range.

Treatment
An airway must be established and maintained. Adequate oxygenation and ventilation must be ensured. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Treatment may include one or more of the following therapeutic interventions: correction of electrolyte abnormalities and acid-base balance, lidocaine, phenytoin, isoproterenol, ventricular pacing, and defibrillation. Disopyramide, procainamide, and quinidine may produce additive QT-prolonging effects when administered to patients with acute overdosage of Mellaril and should be avoided (see WARNINGS and CONTRAINDICATIONS). Caution must be exercised when administering lidocaine, as it may increase the risk of developing seizures.

Treatment of hypotension may require intravenous fluids and vasopressors. Phenylephrine, levarterenol, or metaraminol are the appropriate pressor agents for use in the management of refractory hypotension. The potent adrenergic blocking properties of the phenothiazines makes the use of vasopressors with mixed and adrenergic agonist properties inappropriate, including epinephrine and dopamine. Paradoxical vasodilation may result. In addition, it is reasonable to expect that the -adrenergic-blocking properties of bretylium might be additive to those of Mellaril, resulting in problematic hypotension.

In managing overdosage, the physician should always consider the possibility of multiple drug involvement. Gastric lavage and repeated doses of activated charcoal should be considered. Induction of emesis is less preferable to gastric lavage because of the risk of dystonia and the potential for aspiration of vomitus. Emesis should not be induced in patients expected to deteriorate rapidly or those with impaired consciousness.

Acute extrapyramidal symptoms may be treated with diphenhydramine hydrochloride or benztropine mesylate.

Avoid the use of barbiturates when treating seizures, as they may potentiate phenothiazine-induced respiratory depression.

Forced diuresis, hemoperlusion, hemodialysis and manipulation of urine pH are of unlikely benefit in the treatment of phenothiazine overdose due to their large volume of distribution and extensive plasma protein binding.

Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®**.

DOSAGE
Since MeIlaril (thioridazine HCI) is associated with a dose-related prolongation of the QTc interval, which is a potentially life-threatening event, its use should be reserved for schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. Dosage must be individualized and the smallest effective dosage should be determined for each patient (see INDICATIONS and WARNINGS).

Adults
The usual starting dose for adult schizophrenic patients is 50-1 00 mg three times a day, with a gradual increment to a maximum of 800 mg daily if necessary. Once effective control of symptoms has been achieved, the dosage may be reduced gradually to determine the minimum maintenance dose. The total daily dosage

ranges from 200-800 mg, divided into two to four doses.

Pediatric Patients
For pediatric patients with schizophrenia who are unresponsive to other agents, the recommended initial dose is 0.5 mg/kg/day given in divided doses.. Dosage may be increased gradually until optimum therapeutic effect is obtained or the maximum dose of 3 mg/kg/day has been reached.

HOW SUPPLIED
Mellaril(thioridazine HCI) Tablets
10mg
Bright chartreuse, coated tablets; **"A'** imprinted on one side, "78-2" imprinted on the other side, in black.
Bottle of 100 (NDC 0078-0002-05)
Bottle of 1000 (NDC 0078-0002-09)
Unit-dose package of 100 (NDC 0078-0002-06)
15mg
Pink, coated tablets; imprinted on one side, "78-8" imprinted on the other side, in black.
Bottle of 100 (NDC 0078-0008-05)

25mg
Light tan, coated tablets; imprinted on one side, "MELLARIL 25" imprinted on the other side, in black.

Bottle of 100 (NDC 0078-0003-05)
Bottle of 1000 (NDC 0078-0003-09)
Unit-dose package of 100 (NDC 0078-0003-06)

50mg
White, coated tablets; imprinted on one side, "MELLARIL 50" imprinted on the other side, in black.

Bottle of 100 (NDC 0078-0004-05)
Bottle of 1000 (NDC 0078-0004-09)
Unit-dose package of 100 (NDC 0078-0004-06)

100mg
Light green, coated tablets; imprinted on one side, "MELLARIL 100" imprinted on the other side, in black.

Bottle of 100 (NDC 0078-0005-05)
Bottle of 1000 (NDC 0078-0005-09)
Unit-dose package of 100 (NDC 0078-0005-06)

150mg
Yellow, coated tablets;" imprinted on one side, "MELLARIL 150" Imprinted on the other side, in black.
Bottle of 100 (NDC 0078-0006-05)
200 mg
Pink, coated tablets, imprinted on one side, "MELLARIL 200" imprinted on the other side, in black. Bottle of 100 (NDC 0078-0007-05)
Unit-dose package of 100 (NDC 0078-0007-06)
Store and Dispense
Below 86°F (30°C); tight container.
Mellaril® (thioridazine HCI) Oral Solution (Concentrate)
30 mg/mL
A clear, straw-yellow liquid with a cherry-like odor. Each mL contains 30 mg thioridazine hydrochloride, USP, alcohol, 3.0% by volume. Immediate container: amber glass bottles of 4 fl. oz. (118 mL) as follows: 4 fi. oz. bottles, in cartons of 12 bottles, with an accompanying dropper graduated to deliver 10 mg, 25 mg, and 50 mg of thioridazine hydrochloride, USP (NDC 0078-0001-31).

100 mg/mL
A clear, light-yellow liquid with a strawberry-like odor. Each mL contains 100 mg thioridazine hydrochloride USP, alcohol, 4.2% by volume. Immediate container: amber glass bottles of 4 fi. oz. (118 mL), in cartons ol 12 bottles, with an accompanying dropper graduated to deliver 100 mg, 150 mg, and 200 mg of thioridazin hydrochloride, USP (NDC 0078-0009-31).

Store and Dispense
Below 86°F (30°C); tight, amber glass bottle.

The oral solution (concentrate) may be diluted with distilled water, acidified tap water, or suitable juices. Each dose should be so diluted just prior to administration — preparation and storage of bulk dilutions is not recommended.

MellariI-S (thioridazine) Oral Suspension
5mg/mi
An off-white suspension with a buttermint taste and a peppermint odor. Each mL contains thioridazine, USI equivalent to 5 mg thioridazine hydrochloride, USP. Buttermint-flavored in pint bottles (NDC 0078-0068-33
20 mg/ml
A yellow suspension with a buttermint taste and a peppermint odor. Each mL contains thioridazine, USP, equivalent to 20 mg thioridazine hydrochloride, USP. Buttermint-fiavored in pint bottles (NDC 0078-0069-3
Store and Dispense
Below 77°F (25°C); tight, amber glass bottle.

Additional information available to physicians.

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DATE

ATTACHMENT

PROPOSED "DEAR DOCTOR" LETTER

IMPORTANT
DRUG
WARNING

Dear Doctor:

This communication is to advise you of important labeling changes for all dosage forms of Mellaril® (thioridazine HCl). Based on discussions with the Food and Drug Administration (FDA), Novartis has made the following major modifications to the labeling for these products:

- A boxed WARNING has been added to prominently advise clinicians that Mellaril has been shown to prolong the QTc interval in a dose related manner, and drugs with this potential, including Mellaril, have been associated with torsade de pointes-type arrhythmias and sudden death.
- Mellaril is now indicated only for schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects. Mellaril has not been systematically evaluated in controlled trials in treatment refractory schizophrenic patients and its efficacy in such patients is unknown.

- Mellaril is now contraindicated with certain other drugs, including fluvoxamine, propranolol, pindolol, any drug that inhibits the cytochrome P450 2D6 isozyme, e.g., fluoxetine and paroxetine, and agents known to prolong the QTc interval; Mellaril is also contraindicated in patients known to have reduced levels of the cytochrome P450 2D6 isozyme as well as in patients with congenital long QT syndrome or a history of cardiac arrhythmias;

- Patients being considered for treatment with Mellaril should have a baseline ECG performed and serum potassium levels measured. Serum potassium should be normalized before starting treatment and patients with a QTc interval greater than 450 msec should not receive Mellaril. Periodic ECG's and serum potassium levels during Mellaril treatment may be useful and Mellaril should be discontinued in patients who are found to have a QTc interval over 500 msec.
- Treatment of Mellaril overdosage should entail immediate cardiovascular monitoring, to include continuous electrocardiographic monitoring to detect arrhythmias. Drugs that may produce additive QT-prolonging effects, such as disopyramide, procainamide, and quinidine, should be avoided in the treatment of Mellaril overdosage.

These changes to the product labeling are based primarily on the FDA's review of three published studies

The first of these investigations, a randomized, double-blind, three-period crossover study in nine healthy males following single dose exposure to placebo or one of two thioridazine doses (10 mg or 50 mg), with a one week or longer washout between treatment periods, showed cardiac effects related to the plasma concentration of thioridazine and its metabolites. Among these, this study reported a dose-related prolongation of the QTc interval between 2 and 8 hours after thioridazine administration. Following dosing with thioridazine 50 mg, the mean QTc increased from 388 (SD±18) to 411 (SD±14) msec four hours post-dose, with a mean maximal increase of 23 msec. This change was statistically significantly greater than that for either placebo or thioridazine 10 mg (<0.01 and <0.05, respectively).'

The second recent study demonstrated altered pharmacokinetics and increased serum levels of thioridazine in patients with a genetic defect resulting in slow hydroxylation of debrisoquin. This genetic defect is present in about 7% of the Caucasian population. This study examined results from a single 25 mg oral dose of thioridazine in 19 healthy subjects: 6 slow and 13 rapid hydroxylators of debrisoquin. The slow hydroxylators obtained higher serum levels of thioridazine with a 2.4-fold higher Cmax and a 4.5-fold larger AUC associated with a twofold longer half-life compared with that of the rapid hydroxylators.2

The rate of debrisoquin hydroxylation appears to depend on the activity level of the cytochrome P450 2D6 isozyme. Thus, this study suggest that the co-administration of Mellaril with drugs that inhibit this isozyme and the use of Mellaril in patients with reduced levels of activity of this isozyme will result in substantial elevation of thioridazine plasma levels.

The third recent study evaluated the effect of fluvoxamine *(25* mg bid for one week) on thioridazine steady state concentration in 10 male inpatients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased three-fold following coadministration of fluvoxamine.3

Prolongation of the QTc interval has been associated with torsade de pointes-type arrhythmias and sudden death. There are several published case reports of torsade de pointes and sudden death associated with thioridazine treatment. A causal relationship between these events and thioridazine therapy has not been established but, given the ability of thioridazine to prolong the QTc interval, such a relationship is possible.

Since the degree of QTc interval prolongation appears to be related to the dose of thioridazine, it is reasonable to assume that concomitant medications or other factors, which produce elevations in thioridazine plasma levels, will increase the degree of QTc prolongation and possibly increase the risk of serious ventricular arrhythmias. In addition, the co-administration of Mellaril with other drugs that prolong the QTc interval is expected to produce additive prolongation of the QTc interval. Therefore, the co-administration of Mellaril with inhibitors of cytochrome P450 2D6, e.g., fluoxetine and paroxetine, drugs that prolong the QTc interval, fluvoxamine, propranolol, or pindolol is now contraindicated. For the same reason, Mellaril is also contraindicated in patients known to have reduced levels of cytochrome P450 2D6.

Furthermore, patients with congenital long QT syndrome or a history of cardiac arrhythmias may be at

increased risk for cardiac arrhythmias in the context of thioridazine- associated QTc interval prolongation. Thus, Mellaril is contraindicated in such patients as well.

Patients currently being treated with Mellaril should be fully informed of the above information. Switching to a different antipsychotic agent should be considered and a decision regarding continuation of Mellaril treatment should be based on a careful assessment of the potential benefits and risks of Mellaril for each patient. Please note that mesoridazine, the active ingredient of Serentil®, is the major active metabolite of Mellaril and also appears to have the capacity to prolong the QTc interval.

Please see the enclosed revised package insert for complete prescribing information.

Sincerely,

Novartis signature

Title

[Please insert the above labeling changes here.]

Novartis is committed to providing you with the most current product information available for the management of patients receiving Mellaril. You can further our understanding of adverse events by reporting all cases to Novartis Pharmaceuticals Corporation, 59 Route 10, East Hanover, New Jersey 07936 by phone (888) NOW-NOVARTIS or (888-669-6682) or the internet at: http://www.novartis.com or to the FDA Program by phone at 1-800-FDA-1088, by fax 1-800-FDA-0178, by mail (using a postage-paid form) MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857; or the internet at www.FDA.gov/medwatch.